REIRRADIATION WITH CONCURRENT CHEMOTHERAPHY FOR LOCOREGIONALLY UNRESECTABLE RECURRENT HEAD AND NECK CANCER

Dissertation submitted in partial fulfillment of

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CERTIFICATE

This is to certify that **DR.R.DURGA PRASAD** has been a postgraduate student during the period May 2013 to March 2016 in the Department of Radiotherapy, Madras Medical College, Rajiv Gandhi Govt. General Hospital, Chennai.

This Dissertation titled **"REIRRADIATION WITH CONCURRENT CHEMOTHERAPHY FOR LOCOREGIONALLY UNRESECTABLE RECURRENT HEAD AND NECK CANCER"** is a bona fide work done by her during the study period and is being submitted to The TamilNadu Dr. M. G. R Medical University in partial fulfillment of M.D Branch IX Radiotherapy Examination.

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DECLARATION

I hereby declare that the dissertation entitled **"REIRRADIATION WITH CONCURRENT CHEMOTHERAPHY FOR LOCOREGIONALLY UNRESECTABLE RECURRENT HEAD AND NECK CANCER"**

submitted for the Degree of Doctor of Medicine in M.D., Degree Examination, Branch IX, RADIOTHERAPY is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or Institution for the award of any degree or diploma.

Place: Chennai Signature of the Scholar

Date:

(Dr. R.DURGA PRASAD)

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CONTENTS

TITLE: REIRRADIATION WITH CONCURRENT ORAL CAPECITABINE FOR LOCOREGIONALLY UNRESECTABLE RECURRENT HEAD AND NECK CANCER

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BACKGROUND: Local recurrence is the major cause of treatment failure in head and neck cancer patients and 50-60% of patients die as a direct consequence of recurrent disease. These recurrent tumours is also associated with significant problems related to symptom control and markedly reduces quality of life.

AIMS AND OBJECTIVES: To assess the immediate locoregional response rates and acute toxicities of the treatment of unresectable locoregionally recurrent squamous cell carcinomas of the head and neck treated with reirradiation and oral capecitabine.

MATERIALS & METHODS: The study was conducted in **MMC, BIRO, RGGGH** including **30** Eligible patients were selected for re-irradiation in case of inoperable and/or unresectable tumours treated with conventional fractionation 2Gy per fraction for 5 days a week, up to a total cumulative dose of 120Gy including the previous RT dose with T.Capecitabine 500mg BD on treatment days.

RESULTS: The median time between the first course of radiotherapy and second was 20 months. The overall response rate in our study was 90% including 16 patients with a complete response, 11 patients with a partial response and 3 patients with stable disease. Grade 2 and 3 pharyngeal toxicities noted in 13 and 11 cases respectively. Grade 3 mucositis occurred in 6 patients. The cumulative median lifetime dose was 116 Gy.

CONCLUSION:
This is the first prospective single institutional trial testing reirradiation plus chemotherapy for recurrent SCCHN in our BIRO, RGGGH. We conclude that reirradiation with chemotherapy up to a total dose of 60GY is feasible and effective in carefully selected patients with acceptable acute toxicities.

KEY WORDS: REIRRADIATION, CAPECITABINE, RECURRENCE, UNRESECTABLE HEAD AND NECK CANCERS, MUCOSITIS, DYSPHAGIA.

INTRODUCTION

Cancer is a complex genetic disease derived from the accumulation of various genetic changes. These genetic alterations include activation of proto oncogenes and inactivation of tumor suppressor genes. A number of specific genetic events have been identified in the progression of head and neck squamous cell carcinoma (HNSCC). It has been estimated that up to 10% of all cancers have a strong hereditary component. A clustering of oral cancer has been seen in certain ethnic groups, and an increased risk of cancer has been noted among relatives of patients with one head and neck cancer. Several studies have suggested a threefold higher risk of developing an oropharyngeal cancer in populations that have a first-degree relative with HNSCC.

In a developing country like India there is phenomenal improvement in medical and research field over the past years. The noninfectious diseases becomes the majority cause for morbidity and mortality. The infectious diseases on a downfall path comparing to the noninfectious diseases. In India cancer is increasingly occurring among the adults. Especially head and neck cancers among the younger and older adults.

These cancers occur according to the geographical area and environmental factors. There is a gross variation of occurrence in population. The incidence remains high in the developed countries. Comparing to developed countries the incidence of head and neck cancer remains in the higher side. In India the most common head and neck malignancies are those of oral cavity and pharynx. Oral cavity and pharynx cancers stand as third most common cancer in males and as the fourth common cancer in females in developing countries

The primary reason for increased occurrence of head and neck cancer was tobacco chewing and smoking. The increasing number of cancers results in mortality. Increased risk of buccal mucosa and oropharyngeal cancers occurs in persons using tobacco products. Betel nut chewing and tobacco produces morbidity which influence the quality of life. The effect of alcohol and tobacco also influence the development of head and neck cancers. Pipe and cigar smokers have high incidence of lip and oral cavity cancers because of concentrated carcinogens in these regions.

In summary, the poor socio economic status, oral consumption of tobacco in various forms, use of lime with betel nuts and betel leaf, smoking and alcohol intake together contribute to two lakh cases of head and neck cancer per year in India.

GENETICS:

An emerging area of study centers on the prevalence of specific polymorphisms in enzymes that are involved in the detoxification of several tobacco smoke–derived carcinogens. One larger study of 162 patients with head and neck cancer and 315 healthy controls suggested that certain glutathione S-transferase (GST) genotypes represented independent risk factors for head and neck cancer. Some studies also have shown a two- to three fold risk for the GSTM1 and GSTT1 null genotypes, whereas others have shown no increase in HNSCC risk. Others also have found that the repair capacity of peripheral lymphocytes or their ability to repair carcinogen-induced chromatic breaks may also define a certain risk for head and neck cancer. Cytogenetic approaches have given us some insights into potential areas of deletion and amplification involved in the progression of head and neck cancer. Short-term cultures of primary tumors have proven more reliable for the assessment of complex, chromosome abnormalities and rearrangements. These studies have already demonstrated consistent chromosomal abnormalities and the presence of important alterations. . Studies have shown that p63 is amplified and that Np63 isotypes are overexpressed in HNSCC and enhance oncogenic growth in vitro and in vivo. P53 appears to regulate its family member by physically binding with

Np63 and mediating its degradation. A report has demonstrated that Np63 associates with the B56 regulatory subunit of protein phosphatase 2A and glycogen synthase kinase-3 (GSK3), leading to a dramatic inhibition of protein phosphatase 2A–mediated GSK3 reactivation. The inhibitory effect of Np63 on GSK3 mediated a decrease in phosphorylation levels of -catenin, which induces intra nuclear accumulation of -catenin and activates -catenin–dependent transcription. These results suggest that Np63 isotypes act as positive regulators of the -catenin signaling pathway, providing a basis for their oncogenic properties in SCC.

RATIONALE FOR PRESENTATION IN ADVANCED STAGES:

In India around 50-60% of head and neck cancers present in locally advanced stage. In our institute 60- 75 % patients present with advanced stage. The reason behind this involves various factors influencing the occurrence of head and neck cancers. Some predicted factors are poor socioeconomic status, lack of awareness. Some social factors include education, transport facilities and nosocomephobia.

Kumar. S et al. stated some psychosocial beliefs like

1. Cancer a curse.

2. Ill-fated to have cancer.

3. Trivial ulcers in the mouth are self-limiting.

4. The fear that the prolonged treatment will render the family stressful.

Main important thing was patient attenders advising the patients to seek local treatment and unrecognised treatment practices. Most of the patients land up with advanced stages with increased tumour growth. They seek medical attention after increased tumour burden to the higher centres.

HISTOPATHOLOGY

Squamous cell carcinomas constitute most common variety of histology. Its variants like

1. Lymphoepithelioma.

2. Spindle cell carcinoma.

3. Verrucous carcinoma.

4. Undifferentiated carcinoma.

The less common histology includes

5. Lymphoma.

6. Small cell neuro endocrine carcinoma.

7. Extramedullary Plasmacytoma.

8. Mucoepidermoid carcinoma.

9. Adenoid cystic carcinoma.

10. Melanomas.

Squamous cell carcinomas constitute 97% of cancers in our institute.

TREATMENT OVERVIEW:

The treatment of locally advanced head and neck carcinomas include

1. Surgery.

2. Radiotherapy.

3. Chemotherapy.

These modalities depends on site of tumour, histology and patient preferences. The functional outcome, resect ability, general condition of the patient has a additive factor. Hence despite recent advances the management remains a great challenge.

SURGERY VS RADIATION:

These are the main treatment modalities used in H&N carcinomas. The chemotherapy added to enhance the effect of radiation treatment.

The advantages of surgery compared to radiotherapy are

1. Only limited amount of tissue is exposed to treatment.
2. Shorter treatment time.
3. Acute and late radiation sequel can be avoided.
4. Radiation can be reserved for future recurrences or second primaries.

The most important advantage of radiation therapy compared to surgery

1. Organ preservation
2. Function preservation.

Comparing to elective treatment of neck nodes, elective irradiation of neck can be done with little added morbidity. If radiation fails there is always option of salvage surgery. In surgical failure recurrence occurs at the scar site. It is difficult to distinguish from normal surgical scarring. Hence the diagnosis is often delayed. Re-excision is also difficult under these circumstances.

CONCURRENT CHEMO RADIATION

Concurrent chemoradiation is associated with improved loco regional control and overall survival. The use of chemotheraphy will potentiate the effect of radiation. A recent update of Meta- analysis of chemotherapy on head and neck cancer (MACH-NC) showed [CCRT vs RT]

1. Adding chemotherapy along with radiation results in 19 % reduction in risk of death.
2. 8% improvement in overall survival.

Majority of these benefits are derived from concurrent chemo radiation. The 2 % improvement in survival by induction chemotherapy is not statistically significant. Even though concurrent chemo radiation increases the toxicities of radiation, it exerts a good loco regional and systemic control.

RECURRENCE SETTING:

Local recurrence is the major cause of treatment failure in head and neck cancer patients and **50-60%** of patients die as a direct consequence of recurrent disease. These recurrent tumours is also associated with significant problems related to symptom control and markedly reduces quality of life.

As most recurrences occur in the first **2yr** after primary treatment and **80%** arise in previously high dose irradiated volumes, it is obvious that the management of these recurrences is a challenging clinical problem. If resectable, surgery is the treatment of choice for these lesions and salvage rates tend to vary based on the site of primary. Due to tumour location and extent, surgery is often irradical with close or positive margins. The risk of morbidity is also higher as a result of radiation induced tissue changes which complicate tissue healing.

Only 15-20% of patients will be able to undergo salvage surgery because of the extent of the disease, medical contraindications or patient refusal and also radiation induced changes which complicate healing. Palliative chemotherapy comprises only the management for previously irradiated, unresectable recurrent head and neck cancer. This approach has offered limited palliation with medial survival ranging between 5 and 9 months. Patients receiving supportive care alone have a poor median survival, between **3 and 5 months.**

Therefore Salvage therapy options for patients with unresectable, previously irradiated squamous cell carcinoma of the head and neck (SCCHN) are limited It is important to know that a reduction in tumour size in those cases may still improve quality of life. The median survival time using chemotherapy alone does not exceed 6 months. This suggests the need for new therapeutic approaches.

The agent which increases the efficacy of the reirradiation without considerable toxicity must be selected. **Capecitabine** is orally available, which has shown remarkable efficacy in combination with radiotherapy. The conversion of **capecitabine** to its active metabolite depends on the enzyme thymidine phosphorylase, which is expressed in tumours at a higher level than in normal tissue. In addition, irradiation increases the expression of thymidine phosphorylase in tumors, further enhancing the local activity of capecitabine within the irradiated tumor volume. These properties of **capecitabine** make it an ideal combination partner for achieving a topographically restricted sensitizing effect within the irradiated area.

CHEMOTHERAPY FOR RECURRENT OR METASTATIC DISEASE:

Patients with recurrent or metastatic head and neck SCCs have a median survival of 6 to 9 months, and a 1-year survival rate of 20% to 40% when treated with chemotherapy alone. The survival benefit associated with the use of chemotherapy compared to best supportive care only in these patients has not been well studied. Although selected patients may derive apparent significant prolongations in survival, average survival improvements appear small at best. Morton et al. reported a 2-month improvement in median survival after treatment with cisplatin, with or without bleomycin, compared with no treatment. The duration of responses is typically measured in weeks to months, not years; survival beyond 2 years is infrequent; cures are anecdotal. Thus, the primary intent of chemotherapy in this setting is to achieve tumor regression with the hope that the potential palliative benefit and possible modest survival improvement will outweigh the side effects of treatment. Unfortunately, most clinical trials have historically used response rate and toxicity reporting as surrogate measures for outcomes of greater priority to the patients, such as palliation of specific symptoms (e.g., pain), improvement in function (e.g., swallowing), or overall quality of life.

A number of drugs have been demonstrated in clinical trials to have activity in head and neck SCCs, and the list is well summarized in prior reviews. The most

commonly used include methotrexate, cisplatin, carboplatin, 5-fluorouracil, paclitaxel, and docetaxel, with reported major response rates ranging from 15% to 42%. Among other drugs with reported major response rates of 15% or greater are bleomycin, cyclophosphamide, doxorubicin, hydroxyurea, ifosfamide, irinotecan, oral uracil, and ftorafur (with leucovorin), pemetrexed, vinblastine, and vinorelbine. Some of these agents (e.g., cyclophosphamide, doxorubicin, hydroxyurea) have their activity based on reported assessment in a limited number of patients from over 2 decades ago, an era when methods and criteria for response assessment may have differed from current standards. Anticipated response rates and toxicity profiles may vary based on patient selection and drug schedule. Poor performance status is associated with both lower response rates and greater potential for toxicity. The larger the amount of prior treatment also adversely affects response rates.

Methotrexate is a historic standard drug used in the recurrent or metastatic disease setting. The typical standard dosing is 40 mg/m^2 intravenously weekly, with dose attenuation or increase (up to 60 mg/m^2) based on toxicity, with mucositis being a frequent reason for dose adjustment. The favorable side effect profile and convenience of administration of methotrexate make it well suited for use in this patient population in which medical comorbidity is common, as is more advanced age. Higher doses have been compared to standard dosing in

randomized trials: response rates increase as dose toxicity, without a significant improvement in overall survival. Similarly, newer analogues of methotrexate (e.g., edatrexate) have not been shown in phase 3 trials to offer a therapeutic advantage.

Cisplatin is a cornerstone drug in the modern management of head and neck cancer. Cisplatin is customarily dosed at 75 to 100 mg/m^2 intravenously every 3 to 4 weeks. The potential for renal (i.e., increase in creatinine, electrolyte abnormalities), otologic (i.e., high-frequency hearing loss, tinnitus), neurologic (i.e., peripheral neuropathy), and gastrointestinal (i.e., nausea and vomiting) toxicity are widely appreciated, but these risks are manageable if patients are appropriately screened for therapy, monitored closely during it, and state of the art antiemetics are applied. Further dose escalation of cisplatin has not been established to improve outcome. A randomized trial comparing 60 mg/m^2 versus 120 mg/m^2 of cisplatin failed to demonstrate a significant improvement in response or survival. Carboplatin is the best studied and most commonly used platinum analogue in head and neck cancer. It has less renal, otologic, neurologic, and gastrointestinal toxicity than the parent drug, and is also easier to administer. The tradeoff is that it is more bone marrow-suppressive and may be somewhat less active. This last issue is more of a concern in the definitive treatment setting in which cure is a central end point, as opposed to the palliative setting, when patients often seek a less toxic alternative treatment. Although taxanes as a class have

significant activity in head and neck SCCs, hopes of clinically significant improvement in survival in the palliative setting with the introduction of these agents have yet to be realized. Neither paclitaxel or docetaxel has been demonstrated in random assignment trials to be clearly superior to methotrexate with regard to survival as an end point. Initial studies with paclitaxel used a dose of 250 mg/m^2 intravenously over 24 hours with growth factor support. In an Eastern Cooperative Oncology Group (ECOG) trial, 12 of 30 patients (40%) had a partial (8 patients) or complete (4 patients) response. However, grade 3 or greater neutropenia occurred in 91% of patients, and there were two deaths. Less cumbersome to administer and less toxic schedules are commonly used in practice (e.g., 135–225 mg/m^2 intravenously over 3 hours every 3 weeks; 80–100 mg/m^2 weekly), although their relative efficacies have not been well evaluated. A paclitaxel schedule that provides more prolonged exposure to the drug may be more efficacious, although a phase 2 trial of 120 to 140 mg/m^2 every 96 hours yielded disappointing results even in treatment-naïve patients (major response rate, 13%). Other toxicities, besides myelosuppression, include sensory neuropathy, alopecia, allergic reactions, and arrhythmia, although cardiac monitoring is not required.

Docetaxel appears less neuropathic than paclitaxel, but fluid retention and hematologic toxicity may be more problematic. A typical dose is 60

to 100 mg/m^2 intravenously over 1 hour. Initial studies evaluated the efficacy of the 100 mg/m^2 dose level, with major response rates ranging from 21% to 42% an excellent performance status is required for this higher dose. Lower doses may offer similar efficacy and better tolerance. A multicenter study evaluating a 60 mg/m^2 dose level reported a major response rate of 22%. As with paclitaxel, weekly schedules are applied in practice, but the relative efficacy of a weekly versus every-3-weeks schedule is not well studied. Although initial studies evaluated a bolus schedule for 5-fluorouracil, an infusional program of 1,000 mg/m^2/day over 96 to 120 hours appears more efficacious in head and neck cancer. Infusional 5-fluorouracil is associated with more mucositis and diarrhea than a bolus schedule, so the shorter infusion (i.e., 96 hours) is typically applied in patients who are pretreated and have received prior head and neck RT.

EGFR is highly expressed in most head and neck SCCs, and the degree of expression is inversely associated with prognosis. As such, there has been keen interest in drugs that target the receptor itself or steps downstream. Cetuximab, a chimeric immunoglobulin G antibody that binds the receptor, has been approved by the U.S. Food and Drug Administration for use in patients with disease refractory to platin-based therapy. As summarized in Table 72.7, the response rates in this refractory setting are similar, 10% to 13%, whether cetuximab is used alone

or combined with platin-based therapy. Disease stabilizations were more common, but median survivals remained disappointing, ranging from 5.2 to 6.1 months. The small molecule tyrosine kinase inhibitors gefitinib and erlotinib offer no efficacy advantage in similar refractory patients. Major response rates and median survivals ranged from 0% to 15% and 5.9 to 8.1 months, respectively. A large randomized trial (486 patients) compared gefitinib (250 or 500 mg daily) to methotrexate and demonstrated no survival improvement with either gefitinib dose. There were more tumor hemorrhage-type events on the gefitinib arms (8.9% and 11.4% vs. 1.9%).

REVIEW OF LITERATURE

CONVENTIONAL FRACTIONATION:

Radiotherapy alone has been the standard nonsurgical therapy for locally advanced disease. The conventional fractionation uses 200 cGy per fraction as a standard universal dose for head and neck cancers. Five fractions per week is used and two days of no fractions for patient and physician convenience. Total dose of 60 to 70 Gy is used in 2D technique for all patients with head and neck cancers. This was started by Fletcher without any strong radiobiological basis. It provides acceptable compromise between tumour control and normal tissue complications. In order to improve the therapeutic ratio, the tumour control probability should be increased and normal tissue complication probability should be decreased. In order to achieve this target people started trying modified fractionation.

CHEMO RADIATION:

Most trials used sequential or induction chemotherapy followed by radiotherapy. The Department of Veterans Affairs Laryngeal Cancer study Group

conducted a study. The study comprises locally advanced laryngeal cancer with the purpose of showing feasibility of chemotherapy. The study comprises two arms.

1. Induction chemotherapy followed by radiotherapy with surgery reserved for residual or recurrent lesions

VS

2. Surgery followed by post- operative radiotherapy.

Control arm received three cycles of induction chemotherapy [CDDP+5FU]. The patients were assessed after two cycles of chemotherapy. Any patient who failed to attain partial response→ immediate surgery → radiotherapy. Other patients were allowed to complete three cycles of chemotherapy → radiotherapy.

RESULTS: Overall survival was same in both arms. The 3 year survival rate was 52%. The loco regional recurrences were greater in the control arm (13% vs 3% p=0.001). Salvage surgery in recurrent cases produce no difference in overall survival. Distant relapses were decreased in the chemo arm (12 % vs 18 % p=0.001). Overall survival could not be improved in chemotherapy arm. 75% in the chemotherapy arm retained functional larynx.

CONCURRENT CHEMORADIATION

CCRT: In the evolution of curative radiation treatment CCRT plays an important role. Achieving a favorable balance between tumor cell kill and normal tissue

Toxicity is achievable with cure rates. The function and reserve capacity of tissues and organs are impaired result of previous treatment. The increase in the tumor cell kill of reirradiation should be achieved improve the therapeutic index. Therapeutic index involves not only increased tumour cell kill but also decreased toxicities. There are two regions where reirradiation often is combined with concomitant Chemotherapy. 1. Head and neck tumors. 2. Rectal cancer.

Systematic experimental models is used for development of first-line Combinations. Their evaluation through a classic series of clinical trials is warranted. This involves randomized phase III studies. Development of sound combination regimens for reirradiation is just at its beginning. The clinical situation is complicated by more heterogeneous tumors with resistant tissues. With changes in physiological and micro environmental changes over time is in need of new modalities required for treatment approaches.

The combination of radiation therapy and chemotherapy has been shown to be superior. Responses involving the radiation alone in both tumor response and patient survival is having decreased response. New classes of agents are Being developed and rapidly introduced to clinical use.

These agents target one or more of the processes that play important roles in the malignant phenotype. These new drugs include specific antibodies against growth factors or their receptors and small molecules that interfere with signal transduction pathways regulating the cell cycle, gene transcription and survival in cancer cells. Some of the drugs have a single specific target whereas others may have multiple targets. Because the targets of this therapy are processes that are dysregulated only in cancer cells. These agents do not share the same side effects in normal tissues. There is a doubt whether sequential chemo radiotherapy or concurrent chemo radiotherapy is better.

The RTOG trial conducted by Forastiere et al in locally advanced laryngeal cancer. A total of 547 patients were randomly assigned to three groups. The first group received radiotherapy alone. The second group received induction chemo [CDDP+5FU]→radiotherapy. This group was given concurrent chemo radiation using cisplatin. The end point of the study was laryngeal preservation.

At two year proportion of patients with intact larynx.

1. Concurrent chemo radiation arm was 88%.
2. Induction chemo arm (75% p=0.005).
3. Radiation alone arm (70% p=0.001).

The locoregional control.

1. Concurrent arm (78%).
2. Induction arm (61%).
3. Radiation alone arm (56%).

The overall survival was similar in both groups.

The high grade toxicities

1. 82% in concurrent arm.
2. 81 % in induction arm.
3. 61% in radiation alone arm.

This trial established the superiority of concurrent chemo radiation. Although the toxicities were higher in the concurrent chemo radiotherapy arm.

There are certain important issues over superiority of concurrent chemo radiation.

1. Whether in the radiation alone arm adequate dose of radiation is delivered. Improper dosage resulting in decreased effectiveness.

2. Toxicity associated with concurrent chemo radiation. The completion radiation in time should be given utmost importance. Stoppage of radiation during treatment can happen if patient experiences increased toxicities. The chance of accelerated repopulation is very high in this setting. It can adversely affect the outcome of treatment. So selection of optimal schedule for chemo radiation is important. Effective management of toxicities by providing adequate supportive care is most important.

RADIOBIOLOGICAL BASIS OF CONCURRENT CHEMO RADIATION:

The difference between tumour cells and normal tissues is critical for determining the therapeutic ratio. Tumour cells have accelerated cell proliferation, hypoxia and acidity. These are not present in normal cells. Assessment of resistance to radiation and different chemotherapeutic agents are also important. Combination of radiation and chemotherapy should separate the distance of resistance. Independent toxicity is another

strategy that needs to be exploited. Combination of chemotherapeutic drugs along with radiation should increase the toxicities of each other.

Additive effect: Individual cytotoxicity of the drug + individual effect of the radiation→ overall cell killing. Supra additive effect : cell killing in chemo radiotherapy greater than the cell killing by individual cytotoxic agents. This happens when chemotherapeutic agents interact with radiation and potentiates the effects of radiation. Chemotherapy drugs decrease the number the cancer cells by their independent cytotoxicity. Thereby rendering the residual cancer cells more susceptible to radiotherapy. Chemotherapy drugs also acts on microscopic tumour cells in circulation and kills them. This killing prevent distal relapses.

Sensitivity to radiation: 1. Cellular hypoxia

2. Cell cycle age distribution

Chronic hypoxia → amplification of certain oncogenes like ras, c-myc, c-raf-1. These genes are associated with increased resistance to radiation. Also the radiation generates oxygen free radicals which damages DNA. For the production of free radicals oxygen is required. The third mechanism of interaction

of radiation and hypoxia is oxygen fixation hypothesis. The DNA damages made by radiation become permanent in presence of oxygen. This is mainly due to oxidation of DNA repair enzymes which are active only in their reduced form. Thus by combining radiation with a chemotherapeutic drug which is active against hypoxic cells, we can overcome this resistance to radiation.

Most of the chemotherapeutic agents kill proliferating cells in the well oxygenated area. Tumours lies close to capillaries are easily accessible to chemotherapeutic agents. The bulk of the tumour is decreased and the interstitial pressure falls during the killing of well oxygenated cells. This result in opening of closed capillaries and previously hypoxic cells become oxygenated. Since the tumour shrinks, the previously hypoxic areas move nearer to capillaries. Finally the loss of hypoxic cells results in more availability of oxygen to previously hypoxic cells.

REIRADIATION:

There are lot of emerging theme among many of the published series for reirradiation. One among them is long-term survival can

be achieved with re-irradiation for recurrent or new primary head-and-neck cancer, particularly for those with long disease-free intervals between radiation courses and small, isolated lesions.

Surgical resection has been the mainstay of therapy for recurrent head and neck cancers. The low cure rates questions whether the modest benefits have advantage over the increased morbidity and toxicities of the treatment . Surgery can be technically challenging due to difficulties of operating in previously manipulated or irradiated tissue. The proximity to critical structures such as the carotid artery, skull base, esophagus, and trachea plays an important role in resectable lesions to achieve

Adequate response. Surgery in the previous treated area has lot of factors which predicts the outcome of the disease.

1. Poor vascularity.
2. Healing properties of the previously treated area.
3. Incomplete margins.
4. Graft uptake.
5. Facial reconstruction.
6. Requires base skull surgery in advanced lesions in recurrence setting.

In INDIA most of the institutions lack the facilities for base skull surgery. Adequate expertise in the field of surgical oncology is lacking which indirectly leads to under development of advanced techniques.

Another alternative mode of treatment for this recurrent patients is palliative chemotheraphy. First concern about Palliative chemotherapy is , it is not a curative intent. Lot of trails have shown only less survival when compared to the other modes of treatment. One major concern is no established trails or established chemotheraphy present till now to increase the survival rates. There is also lot factors determining the chemotherapy.

1. Penetration of drugs.
2. Resistant to drugs.
3. Toxicities.
4. Availability of drugs in the tumour area.
5. Surrounding changes in the tumour area resisting the drug.
6. Tolerance of the patient.

Inspite of this factors chemotherapy alone has traditionally been considered in this setting. But the response rates have been poor with low survival and locoregional control. Nearly all patients dying of disease progression within months.

Reirradiation has its own advantages and disadvantages in this recurrent head and neck cancer setting. Because of the risks associated with re-irradiation to the head and neck, strafication of patients is needed utmost. The identification of patients who benefit from this approach is much important. However, the selection criteria for re-irradiation remain poorly defined. It vary across institutions among countries and continents. The basic patient characteristics include

1. Performance status.
2. Baseline functioning.
3. Age.

Studies have suggested that baseline organ function is one of the most critical predictors of the outcome after re-irradiation. Re-irradiation dose was the most important prognosticator for overall survival

FACTORS:

1. INTERVAL BETWEEN RADIATION TREATMENT:

   The single most relevant factor is the interval between initial radiation therapy and the previous radiation therapy. The gap between the doses is important as it predicts directly the

   A. Outcome of toxicities.

   B. treatment tolerance

   C. resistant to treatment

   D. dose calculation

      Increased interval between RT courses lower the probability of developing severe complications. The likelihood of local control also decreases. Most trials used interval of 6 months for re-irradiation of recurrent head and neck cancers. If irradiated less than 6months toxicities will be much higher and resistant to radiation and chemotherapy is higher than what we expect.

2. Several studies have also demonstrated the importance of **tumor bulk** at the time of re-irradiation in predicting the outcome. As the environment surrounding the normal tissue is already disrupted the increased tumour burden with hypoxia will lead to decreased tumour control. Hypoxic regions

will be areas of poor penetration for the drugs and decreases the maximum benefit attained from chemotherapy.

3. Another major consideration is the dose received by critical structures. Such as the spinal cord, optic structures, mandible, brain, and carotid arteries. These organs must be protected during the second treatment course. This will help to determine the dose that can be allowed to these structures. A detailed plan of the original treatment is also required for evaluation of the candidate patients. Consideration of late toxicities for providing better quality of life to the patient is utmost importance while practice 2D technique using cobalt 60. The organs involved are going to play a vital role as if their toxicities limit has crossed their tolerance level it will produce life threatening complications.

   A common practice is to assume a previous delivery of 50 Gy to the spinal cord and brainstem during the initial RT, unless the dosimetry records are available and demonstrated otherwise. Many institutions have assumed a 50% dose tolerance recovery of CNS structures if the interval between RT courses is 1 year. This assumption might be conservative and might apply to all tissues not exhibiting clinical levels of radiation injury from the first treatment course.

Decisions regarding re-irradiation should ideally be made in a multidisciplinary setting. Careful review of all imaging studies, and previous radiation fields with dosimetry is needed. Biopsy-confirmed evidence of pathologic recurrent disease is imperative. Because radiographic and clinical suspicion can often be complicated by inflammatory changes.

Appropriate imaging should be done to rule out cartilage necrosis or arytenoid edema from the previous treatment. These complicate the present scenario with high risk of aspiration and/or airway closure. Re-irradiation will not be offered to a patient with known osteoradionecrosis. Severe cervical fibrosis also influence the management with reirradiation in recurrent head and neck cancers. Doses to the mandible should be considered as it can lead to osteoradionecrosis which can complicate the patient his quality of life. Doses can be planned assuming 50% recovery from the previous doses for the present planning doses.

WHY IT IS NEEDED???

Most of this population will die as a direct consequence of uncontrolled tumor growth at the primary site. If left untreated, the prognosis of patients with is poor. The median survival is only a few months. The importance of locoregional control in the setting is unquestioned. For patients with recurrent disease, considerations for additional therapy must be balanced between the prospects of disease control and toxicity. Although the competing risk of developing distant

metastasis is significant, most of this population will die as a direct consequence of uncontrolled tumor growth at the primary site. Studies have shown that if left untreated, the prognosis of patients with locoregionally recurrent head-and-neck cancer is poor, with a median survival of only a few months.

A common practice is to assume a previous delivery of 50 Gy to the spinal cord and brainstem during the initial RT, unless the dosimetric records are available and demonstrated otherwise. On the basis of preclinical data, many institutions have

assumed a 50% dose tolerance recovery of CNS structures if the interval between RT courses is 1 year. This assumption might be conservative and might apply to all tissues not exhibiting clinical levels of radiation injury from the first treatment course.

How much?

Higher the dose delivered, the greater the probability of disease control. Experimental data have suggested that cumulative biologically equivalent doses of #130 Gy. That can be safely tolerated in the recurrent head and neck cancers. Most trials have recommended limiting the cumulative spinal cord dose to 50 Gy. The proximity of the tumor to critical structures must also be considered. Preclinical data have attempted to determine the normal tissue tolerance to reirradiation. Some have suggested that the soft tissue can tolerate approximately 90% of total dose . The dose is heavily dependent on the volume of overlap and the interval between radiation courses. Some research papers evaluated greater 60GY of reirradiation dose can achieve good biological control than the doses <60GY.

TOXICITIES:

During a course of H&N radiation therapy, there are predictable side effects that are experienced by the majority of patients: mucositis, fatigue, loss of taste acuity, radiation dermatitis, and xerostomia. Typically patients will begin to experience mucositis during the third week of radiotherapy. This initially manifests as mucosal blanching within the treatment field, but can progress to patchy or confluent mucositis. Initially patients can be treated with an over-the-counter pain reliever, but once patients develop grade II or III mucositis, they will commonly require narcotic analgesics for adequate pain control.

The combination of dysphagia and mucositis can result in significant nutritional compromise necessitating intravenous hydration and parenteral nutritional supplementation. Nausea associated with treatment can also further complicate the nutritional status. These acute toxicities can become particularly pronounced in the setting of intensified radiation fractionation schedules or combined chemo radiotherapy. Patients may require prophylactic anti emetics. In

patients receiving concurrent radiotherapy and platinum-based chemotherapy, there is clear potential for myelosuppression; therefore, blood counts should be monitored regularly. Signs or symptoms of infection should be addressed promptly. Finally, xerostomia can become problematic during the course of radiation.

Ultimately, patients can be reassured that the majority of these side effects, with the exception of xerostomia, are temporary and will resolve several weeks to months following completion of therapy. As noted, one of the acute side effects of radiotherapy that can become permanent is xerostomia. Chemical and physical modifiers of the radiation response have been utilized to reduce long-term xerostomia.

The free radical scavenger amifostine has the potential to reduce radiation effects on normal tissues if administered just prior to each radiation fraction. A randomized phase III trial demonstrated a reduction in the severity of the acute and chronic grade 2 or higher xerostomia in patients who received amifostine during RT. Dose limiting toxicities commonly include hypotension and nausea. There has been concern over possible tumor-protective effects of amifostine, but a recent metaanalysis does not suggest this. However, data supporting the use of amifostine to reduce xerostomia has been generated in the setting of conventional radiation, and the magnitude of benefit on xerostomia of

parotid-sparing IMRT appears greater than that of amifostine. Therefore, the ultimate value of amifostine in patients with advanced H&N cancer, especially in the setting of IMRT, has been called into question.

Currently there is no universal standard recommendation across treatment centers for the use of this radio protector. In some cases, hypopharynx cancer patients who complete a course of radiation therapy will be noted to have persistent laryngeal edema on subsequent follow-up visits. Although in the early posttreatment phase (in fact up to 24 months), significant or newfound edema should raise suspicion regarding the possibility of persistent or recurrent disease; the majority of patients who receive high-dose radiation across major segments of the larynx and hypopharynx will manifest some degree of edema, mucosal congestion, and eventual fibrosis. Generally, this collateral damage is a tolerable chronic toxicity with modest impact on patient quality of life. However, in approximately 10% to 15% of patients, this edema is severe enough to cause significant airway and swallow function compromise requiring tracheostomy.

DENTAL CARE:

Prior to the initiation of head and neck radiation, a careful oral and dental evaluation, including a panoramic radiograph, should be performed. Dentition in poor condition should be identified and considered for extraction to minimize the subsequent risk of osteoradionecrosis. Specifically, those teeth that will reside within the high-dose radiation volume that demonstrate significant periodontal disease, advanced caries, or abscess formation or are otherwise in a state of disrepair should be extracted. In addition, impacted teeth, unopposed teeth, and teeth that could potentially oppose a segment of a resected jawbone should be considered for extraction if they are anticipated to reside within the high-dose radiation treatment volume. Extraction of marginal teeth should also be considered in patients who are deemed unable to maintain adequate oral hygiene.

Radiation can induce several chronic effects in the oral cavity that warrant routine surveillance. Radiation can impair bone healing and diminish the capacity for successful recovery following trauma or oral surgery. For this reason, elective oral surgical procedures including extractions must be very carefully considered after radiation. Escalation of dental caries deriving from xerostomia following radiation is well recognized. Radiation of the major salivary glands changes the nature of salivary secretions, which can increase the accumulation of

plaque and debris, reduce salivary pH, and reduce the buffering ability of saliva. This creates an environment in the oral cavity, which predisposes patients to caries. During a course of radiation to the oral cavity, simple techniques such as the use of custom molds to absorb electron backscatter can diminish hot-spot mucositis from dental fillings and improve treatment tolerance. Attention to oral hygiene with frequent dental follow-up examinations and cleanings, daily fluoride therapy, flossing, and brushing should be an integral component of the education and post radiation care of patients who undergo radiation to the oral cavity.

PROGNOSTIC FACTORS:

- PRIMARY-site, size, extent& regional / distant Mets
- NODES-single most imp in survival
- HISTOLOGY differentiation-less imp
- PREVIOUS H&N cancer-major
- Cigarette&tobacco-25 fold risk, abstain-30% reduction in 1-9yrs quit, 50% reduction in >9yrs quit
- HPV related – better prognosis regardless of treatment

POST RADIATION DISABILITIES:

- Degree of functional deficits depends on extent and type of radiation therapy
- Side effects – common, directly influence communication and swallowing functions.
- Effects of radiation therapy change over time and may involve mucosal tissue and muscle function.

RADIATION THERAPHY SIDE EFFECTS:

- Severe pain
- Reduced salivary flow,
- Edema
- Restricted movement
- Nausea and vomiting
- Reduced appetite
- Reduced senses of taste and smell
- Dental problems.

POST CHEMO DISABILITIES:

- Post Chemo Disabilities – impaired communication and swallowing functions.
- Fatigue
- Nausea and vomiting
- Loss of appetite
- Reduced senses of taste and smell
- Gastrointestinal irregularities
- Oral dryness and sores in the mouth.

TRACHEOSTOMY ISSUES

- The primary roles of tracheostomy in the treatment of head and neck cancer after surgical interventions are to maintain an open airway and provide access for pulmonary toilet during the recovery period.
- On some occasions, a tracheostomy tube can be placed during or after radiation treatment to alleviate respiratory distress resulting from edema of the airway.
- Placement of a tracheostomy tube reduces airflow and air pressures within the upper aero digestive tract that support speech and swallowing functions.

- Reduction or elimination of expiratory airflow reduces cough effectiveness and disturbs the normal apneic interval during swallowing.
- Placement of a tracheostomy tube has been associated with increased risk of aspiration resulting from disruption to normal swallow biomechanics.
- This procedure may tether the larynx, reducing laryngeal excursion during swallowing.
- A more pronounced tethering effect may result from large-diameter or inflated-cuff tracheostomy tubes.
- Reduction in laryngeal excursion contributes to incomplete clearance of materials from the pharynx during swallowing.
- Subsequently, post-swallow residue can be aspirated.
- Also, use of a high-pressure cuffed tracheostomy tube may increase pressure in the upper esophagus or impinge on the esophagus, causing backflow and aspiration of contents into the airway.
- Patients continue to aspirate around the cuff because of incomplete sealing or leaks after movement or subsequent to large-volume swallows.
- For these reasons, clinicians should exercise caution when initiating oral feeding in patients with a tracheostomy tube with an inflated cuff.

RADIATION THERAPY IMPACT ON SPEECH, VOICE, AND SWALLOWING FUNCTIONS:

- Radiation therapy contributes to a variety of mucosal and muscle tissue changes, which can complicate existing speech, voice, or swallowing difficulties and create new problems.
- Frequent side effects of radiation therapy that may have a negative impact on speech, voice, or swallowing functions include mucositis, xerostomia, and edema.
- As a result of these complications, patients may experience pain, dryness, and limited mobility of structures required for successful speech, voice, or swallowing functions.
- Difficulties that persist after completion of radiation therapy may be linked to fibrosis or atrophy in muscles or peripheral nerve deficits, or both.
- In addition, thickened secretions in the oropharynx, hypopharynx, or larynx alter speech and voice clarity and contribute to reduced swallow efficiency.
- Consequently, reduced swallowing efficiency results in prolonged meal times, post-swallow residue requiring multiple swallows to clear, and difficulty controlling the direction of a swallowed bolus, leading to potential risks of tracheal aspiration.

OROPHARYNGEAL SWALLOWING PROBLEMS ASSOCIATED WITH RADIATION THERAPY FOR HEAD/NECK CANCER :

Bolus control deficits (63%).

Small amounts per bolus.

Multiple swallow attempts per bolus.

Increased mealtimes.

Reduced frequency of swallowing.

Dry mouth (92%).

Pain (58%).

Altered taste (75%).

TOLERANCE LEVELS OF OAR:

Optic nerve and Chiasma	**54 GY**
Brain stem	**54 GY**
Spinal cord	**45 GY**
Temporal lobes	**60 GY**
Inner ear	**50 GY**
Pituitary	**45 GY**
Eyes	**35 GY**
Parotids	**<26 GY in at least 1 gland**

TRAIL:

1. Recently published Phase III multi institutional trial of 130 patients from Europe. Re-irradiation could also have a role in the postoperative setting. The use of postoperative re-irradiation with concurrent 5-fluorouracil and hydroxyurea increased both acute and late toxicity compared with observation alone, a significant improvement in disease-free survival was nevertheless reported with the more aggressive regimen. Given the impressive results of that trial, it might be reasonable to offer re-irradiation to select postoperative patients with high-risk surgical feature such as positive margins or extracapsular nodal spread, depending on other patient characteristics, as previously discussed.

2. The Radiation Therapy Oncology Group trial 96-10 [prospective] of 86 patients. IT includes patients who had undergone primary RT 3 years. 1-year overall survival rate of 48% in >3yrs arm. 1-year overall survival rate of 35% for patients treated within 3 years. The acute and late toxicities however was not insignificant. In the RTOG 96-10 trial, RT was delivered using standard 2D technique. Lateral -opposed, single wedge paired, oblique fields targeting the gross tumor. The margins were generous and it is not similar to that of primary radiation treatment planning CTV. Three-

dimensional planning using computed tomography (CT) was recommended. Similarly, in the series by De Crevoisier et al. all patients were treated by two-dimensional techniques using cobalt-60 beams. RTOG 96-10 treated with 60 Gy at 1.5-Gy, twice-daily fractions. Chemotherapy administered every other week with 5-fluorouracil and hydroxyurea. Although nearly all patients successfully completed reirradiation. Only 6 treatment-related fatalities were reported.

3. Salama et al.

DOSES	3YEAR OVERALL SURVIVAL	LOCOREGIONAL CONTROL
<58GY	6%	33%
>58GY	30%	56%

This study estimated the total reirradiation dose for better outcome. This study states that >58GY needed for achieving the locoregional control.

4. Watkins et al. also showed that re-irradiation doses >58 Gy improved survival.

5. Most of the experimental data have suggested biological equivalent doses.

   A.Cumulative biologically equivalent doses of #130 Gy.

   B.Cumulative spinal cord dose to 50 Gy.

6. De Crevoisier et al. compared three re-irradiation schedules.

   a. conventional fractionation to 65 Gy using 2-Gy fractions (without chemotherapy);

   b. split-course conventional fractionation to 60 Gy. Using 2-Gy fractions delivered on alternating weeks (with concurrent chemotherapy);

   c. split-course hyperfractionated re-irradiation to 60 Gy. Using 1.5-Gy fractions delivered twice daily (with concurrent chemotherapy).

   Given the wide range of patients treated and limited numbers, it was not surprising that no significant differences were observed among these 3 schedules with respect to any of the endpoints analyzed.

AIMS AND OBJECTIVES

AIM OF THE STUDY:

Primary Objective:

To assess the immediate locoregional response rates of unresectable locoregionally recurrent squamous cell carcinomas of the head and neck treated with reirradiation and oral capecitabine.

Secondary Objective(s):

To assess the acute toxicities of the treatment.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study is a prospective single arm study involving previously treated patients with locally recurrent unresectable squamous cell carcinomas of head and neck. Thirty patients with histologically proved squamous cell carcinomas registered in our department were included. The accrual of the patients was started after obtaining consent from the ethical committee for conducting this study in our institute. The informed consent was obtained from all the patients included in the study. The study period was from march 2015 to september 2015.

Subject Selection:

Biopsy proven squamous cell carcinoma of head and neck with performance status ECOG 0-2

INCLUSION CRITERIA:

- Biopsy proven recurrent squamous cell carcinoma of the head and neck
- Primary tumour sites: oral cavity, oropharynx, hypopharynx, larynx
- Without any evidence of distant metastases
- Age 18-60 years
- ECOG performance Status ≤2
- Ineligible for definitive surgical resection
- Anticipated cumulative spinal cord dose will be limited to 50GY
- Maximum prior RT 75GY
- Recurrence appeared atleast 6 months after the end of prior definitive radiotherapy
- Submission of prior radiotherapy records
- Adequate bone marrow, hepatic and renal functions
- No associated comorbidities
- Signed informed consent prior to initiation of protocol specific procedure

EXCLUSION CRITERIA:

- Non squamous histology
- Tumours of the nasal cavity, paranasal sinuses, nasopharynx, salivary glands
- Previously received treatment for any other malignancy
- Inadequate hepatic and renal functions and bone marrow reserve
- Patients not consenting for chemotherapy at any point in the treatment

PRE-TREATMENT WORK UP AND GENERAL MEASURES:

1. Biopsy from tumour

2. Complete blood count, renal and liver function tests weekly

3. CT scan Neck (From Base of Skull to Root of Neck) – Plain and Contrast before start

Of treatment and after completion.

4. Chest X ray – PA view, blood grouping & typing

5. Dental evaluation

STUDY DESIGN: SINGLE ARM PROSPECTIVE STUDY

PATIENT PREPARATION

All patients were advised to quit smoking and alcohol. Studies have shown that smoking and alcohol intake during radiotherapy has shown poor results. Shaving must be done before radiation treatment for uniform distribution of dose.

DENTAL PROPHYLAXIS

Dental prophylaxis has been done in all required patients. It is done in the form of dental filling, scaling and extraction. Prophylactic antibiotics were started 2-3 days prior to the extraction. Then they are maintained on antibiotic coverage for 7 to 10 days. Complete hygiene instruction were given. Precautionary instruction about the premature use of prosthesis and trauma were given.

Patients were instructed to clean their teeth after each main meals. They are advised to use soft brush. They were also instructed to use soda bicarbonate mouth wash. The patients were instructed to prepare mouth wash themselves. They were advised to dissolve one pinch of soda bicarbonate powder to glass of water.

NUTRITIONAL CARE

Patients receiving radiation therapy to head and neck have specific feeding problems. All the patients involved in the study were encouraged to take adequate nutrition. This important care will prevent excessive weight loss.

Ingesting food by mouth is the preferred method of feeding. However nasogastric tube is inserted if required. In extreme cases of concurrent chemo radiation, intra venous hyper alimentation is given.

Specific meal plans were devised for individual patients. The meal plans were maintained as close to the normal diet. Calories equal to normal person diet maintained even when the texture and consistency were changed. The patient's weight was checked on a weekly basis. Weekl evaluation how well the patient is eating. Depending on the weight the meal plans are revised on a weekly basis. The meal plans are advised with increased caloric and protein requirements of the patient. This is important for the regeneration the tissues.

From the third week patients were advised to take mainly liquid diet. Radiation induced reactions will start by 3rd week. The patients with radiation induced dysphagia and mucositis are required specific plan. The specific meal plan was changed to incorporate mainly liquid diet. During the fourth week of radiation xerostomia will be the main cause of dysphagia. The patients will be having difficulty in swallowing solid foods. The dryness of mucosa will cause the solid foods to stick to mucosa and induces vomiting. They are advised to take fresh juices like apple and guava and avoid citrus fruits like lemon and Mozambique. Home- made high protein formula using banana, egg, milk and sugar were advised twice daily.

RADIATION THERAPY:

Patient Set Up:

All patients were treated using Theratron phoenix cobalt unit. Patients were treated in right and left lateral positions.

Target Volume:

Target volume included tumour along with 2 cm clearance.

Portals

Two opposing lateral portals were used.

Dose

Radiotherapy will be delivered by opposing lateral fields with a telecobalt machine in 200cGy per fraction for 5 days a week. Reirradiation up to a cumulative dose of 120Gy including previous RT dose will be given. Oral T.Capecitabine 900mg/m2 in divided doses given on treatment days. Entire treatment is to be completed in less than 7 week time.

CHEMOTHERAPY PROTOCOL

T.CAPECITABINE

Dose	900mg / m^2 daily
Schedule	BD dose on all RT days

PRE TREATMENT ASSESSMENT

Regarding radiation the following toxicities were assessed during every week of radiation.

1. Skin reactions
2. Mucositis
3. Xerostomia
4. Dysphagia
5. Laryngitis

INTRA TREATMENT ASSESSMENT

1. Prior RT dose
2. Prior RT field and extension
3. Prior staging and extension of tumour
4. Prior toxicity assesement
5. Prior chemotherapy

Regarding radiation the following toxicities were assessed during every week of radiation.

1. Skin reactions
2. Mucositis
3. Xerostomia
4. Dysphagia
5. Laryngitis

Regarding capecitabine the following toxicities will be assessed during every week.

1. Nausea
2. Vomiting
3. Abdominal pain

The toxicities were assessed using RTOG Acute Morbidity Scoring Criteria and Common Toxicity Scoring Criteria. The toxicities were assessed every Monday and recorded. All the toxicities are managed according to the guidelines.

For prevention of mucositis all patients were advised to maintain good oral hygiene. Soda bicarbonate mouth wash gargle 5 -6 times a day is advised. Patients were also instructed to apply honey.

a. 15 minutes prior to the radiation.
b. 15 minutes after radiation.
c. 12 hours after radiation.

When patients developed mucositis, they were treated using NSAIDS, steroids and antibiotics. NSAIDS used was Diclofenac tablets 50 mg twice daily. The steroid used was dexamethasone 4 mg IV twice daily when the patients developed grade III toxicities. All patients with grade III mucositis were under broad spectrum antibiotic coverage. In case of grade II pharyngitis and laryngitis patients were treated using NSAIDS and antitussives. In case of all grade III toxicities, steroids were incorporated into management.

Hemoglobin was checked every week. If hemoglobin level goes below 10 g/dl %, the patients were given packed cell transfusion. If the count goes down below normal value. (Absolute neutrophil count below 2000). The patients were given Inj. G-CSF 300 mg sub cutaneous once daily for three days.

RESPONSE ASSESSMENT

Response to the therapy was assessed six weeks after completion of treatment. Both clinical and radiological assessment was done. Response assessment was done using RECIST criteria version 2.0. Assessment of complete response, partial response, no response or progressive disease was done.

All patients with complete response after the protocol were observed on monthly follow up. The patients with residual disease or progressive disease were assessed for salvage surgery.

RESULTS

AGE GROUP	NO. OF PATIENTS
30-40	6
40-50	12
50-60	11
60-70	1

AGE DISTRIBUTION:

The age distribution in our study falls maximum in the age group 40-50 and 50-60. The chronicity of the exposure to tobacco related products and other forms of tobacco are the main causes for this age distribution. The young adults are the group which now in the increasing side of occurrence of head and neck cancers in India.

SEX DISTRIBUTION

SEX	NO. OF PATIENTS
MALE	25
FEMALE	5

Males are the dominant group due to the established cause of tobacco usage in the males comparing to women. In females also pan chewing in the form of areca nuts with leaves are a cause for head and neck cancers.

ECOG PERFORMANCE STATUS

ECOG	NO. OF PATIENTS
1	12
2	18

ECOG performance status is one of important tool in determining the management decision for reirradiation. The tolerance of the patient towards radiation and chemotherapy tolerance are decided by the performance status along with age and other factors.

SITE:

SITE	NO OF PATIENTS
ORAL CAVITY	12
OROPHARYNX	8
HYPOPHARYNX	7
LARYNX	3

The common site of recurrence in our study is oral cavity. Oropharynx hypopharynx larynx falls after oral cavity. Among the oral cavity cancers tongue is the common site of recurrence.

STAGING

r TUMOUR	NO.OF PATIENTS
rT0	00
rT1	00
rT2	12
rT3	16
rT4	02

Stage at which patient presents is an important prognostic indicator for treatment outcome. In our study most of the patients present with T3 and T2 tumour stage. The patients who are all not eligible for surgery are managed with reirradiation. T1 lesions are amenable for surgery with clearance comparing to the t3 and t4 lesions. In most of the single institution trails staging is considered as important prognostic factor. De gustave et al. large single institution trail concluded staging is one of the important predictor for outcome of reirradiation in head and neck cancers.

NODAL STAGING

NODAL	NO.OF PATIENTS
N0	15
N1	09
N2	06

Local recurrence is the most common of failure than comparing the regional recurrence in recurrent head and neck cancers. Regional recurrence with local recurrence is less common presentation comparing to patients presenting either with local recurrence alone or regional recurrence alone.

PREVIOUS TREATMENT:

PREVIOUS TREATMENT	**NO.OF PATIENTS**
RADIATION ALONE	**05**
RADIATION → SURGERY	**03**
SURGERY → RADIATION	**04**
RADIATION + CHEMOTHERAPY	**18**

In our study most of the patients had radiation + chemotherapy as the previous treatment. The radiobiology of the tumour is important such that vascularity perfusion tumour resistance are compared to surgical area will be altered. It also suggest that most of the advanced nature of the diseases recurred.

PREVIOUS CHEMOTHERAPY

CHEMOTHERAPY RECEIVED	NO. OF PATIENTS
WEEKLY CDDP	07
3 WEEKLY CDDP	11
CDDP + 5FU	08
CDDP+ PACLITAXEL	05

There are no solid evidence suggesting the radiobiology of chemotheraphy in recurrent setting. Common factors needed for the chemotherapy in the setting of reirradiation of head and neck cancer is perfusion of the drug, availability in the tumour area, decreased drug resistance, radiosensitive effect, cumulative effect of cell killing [tumouricidal dose] less side effects. Full dose

chemotherapy using cisplatin 5-fu paclitaxel combinations will produce toxicities to the normal tissues in additive with radiation.

RADIATION FRACTIONATION

PREVIOUS FRACTIONATION	NO OF PATIENTS
CONVENTIONAL	19
HYPERFRACTIONATION	08
ACCELERATED	03

Different fractionation schedules in the previous treatment is also an important factor as it can correlate with the late term toxicities. Comparing to conventional fractionation, hyper fractionation is having low bed dose in the normal tissue areas. The late toxicity is low when compared to conventional and other fractionations.

PRIOR RT DOSE

PRIOR RT DOSE	NO. OF PATIENTS
70-80 GY	**05**
60-70 GY	**21**
50-60 GY	**04**
40-50 GY	**01**

The bed dose for the present reirradiation was calculated by using decay factor and formula.

PRESENT BED DOSE= DECAY FACTOR X TOTAL DOSE [PREVIOUS]

DECAY FACTOR = (T/T+R)0.11

GAP BETWEEN RADIATIONS

TIME INTERVAL	NO OF PATIENTS
6MONTHS – 1YEAR	02
1YEAR- 2 YEAR	06
2YEAR -3YEAR	10
>3YEAR	12

The interval between the radiation is one of the important factor determining the tolerance of the treatment and their toxicities. Patients whose treatment interval time greater than three years will tolerate better with another full dose of radiation dose comparing to the other patients interval doses. Reirradiation even after 6months are practiced in some institutions. Most of the trials reirradiate cases after 6months mostly with conformal RT and also with conventional technique.

FEEDING TUBE:

FT REQUIREMENTS	NO.OF PATIENTS
BEFORE RT	08
DURING RT	10
AFTER RT	12

Feeding tube requirements indirectly measures the dysphagia. The patients who needs of the feeding tube after reirradiation were found to be surviving with grade 2 and 3 dysphagia. The patient who requires feeding tube before radiation can be due to late toxicity of previously treated radiation or odynophagia/dysphagia due to tumour extension in the recurrent setting.

TOXICITIES:

We categorized the toxicity of the patient into hematologic and non hematologic. In our study comparing to non hematologic toxicity hematologic toxicity occurred very less percentage. The chemotheraphy used is only produced the GI symptoms like nausea vomiting diarrhea abdominal pain. Radiation treatment is associated mostly with non hematologic toxicities like soft tissue toxicity, mucous membrane and skin.

HEMATOLOGIC:

	GRADE1	GRADE2	GRADE3	GRADE4
NEUTROPENIA	35%	14%	02%	0%
THROMBOCYTOPENIA	25%	0%	0%	0%
LEUCOPENIA	48%	0%	0%	0%

NONHEMATOLOGIC

	GRADE1	GRADE2	GRADE3	GRADE4
SKIN	63%	25%	02%	00%
MUCOSA	70%	21%	01%	00%
SALIVARY GLAND	40%	50%	10%	00%
PHARYNX	45%	43%	12%	00%
LARYNX	60%	35%	05%	00%
DIARRHOEA	40%	-	-	-

In our study non hematologic toxicities comprises the most. The pharyngeal toxicities are the important one influencing the completion of treatment. The quality of the patient was reduced in some of the patients due to the dysphagia. Most of the patients cope with dysphagia with proper counselling and techniques of food intake like change in consistency frequencies matching with the requirement of normal person energy and calories.

MUCOSITIS:

MUCOSITIS GRADE	NO.OF PATIENTS	MEDIAN LIFETIME DOSE
GRADE 0	00	120GY
GRADE 1	15	120GY
GRADE 2	13	110-120GY
GRADE 3	02	110GY
GRADE 4	00	-

The patients who received the mean life time dose of 120 GY had grade 2 mucositis. The grade 3 mucositis occurred in two patients only with 120 GY.

The mean life time dose of 120GY is acceptable and tolerance of the patients is good with less toxicity.

DYSPHAGIA:

DYSPHAGIA	NO OF PATIENTS	MEDIAN LIFE TIME DOSE
GRADE 0	-	-
GRADE 1	15	120 GY
GRADE 2	13	120 GY
GRADE 3	02	120 GY
GRADE 4	-	-

Dysphagia increased in both number of patients and in grades. Patients with grade 2 toxicity occurs with a median life time dose of 120GY. Hence our study represents less toxicity when compared to other single institution study were toxicities remains in the higher side.

ASSESEMENT OF TOXICITIES:

MUCOUS MEMBRANE:

Toxicity assessment was done every week and the results of the 3weekly assessment is shown below:

In our study mucositis present in all the patients but less in severity. The grade 2 mucositis occurred in most of the patients during the 3rd and 6th week. Grade 3 mucositis occurred mostly in the 6th week. There is no occurrence of grade 4 and grade 5 toxicities. Also there is no treatment gap and all patients completed the treatment without interruption. But the patients who was irradiated within 6 months to 1year experienced the grade 3 toxicities. All other patients who underwent reirradiation greater than 2years had less mucositis of grade 2.

PHARYNX:

In our study dysphagia due to involvement of constrictor muscles of pharynx is an important toxicity as it interrupts the nutrition for the patient. The need of feeding tube is mainly due to pharyngeal toxicities. The toxicities are more commonly present in the 3rd and 6th week.

SKIN:

Skin involvement in our study mostly comprises grade 1 and grade 2 during the 3rd and 6th week. The patients were not suffered any skin infection in the grade 3. All the patients were able to tolerate the reirradiation with acceptable toxicity. There is no treatment gap during to the grade 2 toxicity.

SALIVARY GLAND:

XEROSTOMIA was present in most of the patients before starting radiation. This is due to previous exposure of the patient to radiation in 2D technique were sparing of the parotid function less. The impact of dryness of the mouth producing difficulty in swallowing in our patients is less on the completion of the treatment. Because all the patients were accustomed to the xerostomia complications. They were advised good oral hygiene and mouth care. Overall in our study the complications rate were less and patients were reirradiated with acceptable toxicity.

LARYNX:

Laryngeal complications including voice change, laryngeal edema, thyroid cartilage damage were reported less frequently in our study. Most of the patients had voice change during the 3rd and 6th week. The regain voice occurred in more than 75% of the patients. The life threating complications occurred less commonly. We have not encountered any grade 4 or grade 5 complications.

RESPONSE:

RESPONSE	NO. OF PATIENTS (%)
COMPLETE RESPONSE	16 (53%)
PARTIAL RESPONSE	11 (37%)
STABLE DISEASE	03 (10%)
NO RESPONSE	00 (00%)
OVERALL RESPONSE RATE	90%

we assessed the response with RECIST criteria using imaging modality, clinical assessment and with expert opinion from ENT surgeons. In our study complete response was increasingly high when compared to the other comparable single institution trials. We come to know that our study using the reirradiation is superior with good response rate. The patients with partial response had symptom relief with the reirradiation. Most of the patients responded to our treatment except with some 3 patients with stable disease.

COMPARING THE DOSES:

RESPONSE	<60GY	60GY
	NO. OF PATIENTS	NO. OF PATIENTS
COMPLETERESPONSE	2(12%)	14(88%)
PARTIAL RESPONSE	3(27%)	8(73%)
STABLE DISEASE	3(100%)	-
NO RESPONSE	-	-
OVERALL RESPONSE	27%	73%

In our study we also compared the doses in which patients undergone treatment. The patients received 60GY and above had good response when compared to patients received <60GY.

DISCUSSION

DISCUSSION:

We have focused our study on clinical outcome and toxicity. We conclude in our study that reirradiation was feasible in recurrent unresectable head and neck cancers. The acute toxicity was acceptable even if the patient is reirradiated in any intervals of time. In our experience there is a marked increase in then response rate comparing to other metaanalysis and single institution trails. We also come to know that chemotheraphy alone will not produce superior results when comparing to reirradiation. In a study done in Gustave-roussy institute included 169 patients with unresectable head and neck cancers 37% had complete response and 21% overall response rate at 2yrs. The median survival was 10months. The rate of mucosal necrosis and osteoradionecrosis is 5-20% and 1-10% respectively. This study also concluded the incidence and severity of toxicities higher when comparable to primary radiation. Comparing to this study we had superior results with 53% complete response and 37% partial response. The toxicity also occurred less in compared to this study. The acute mucositis grade 3 and grade 4 were higher in the literature 30% and 40% respectively which is more than half percent less in our study. Xerostomia was present in most of the patients before starting radiation. This is due to previous exposure of the patient to radiation in 2D technique were sparing of the parotid function less. The impact of

dryness of the mouth producing difficulty in swallowing in our patients is less on the completion of the treatment Hematological toxicities also low in our study. In other literature studies the grade 3 and grade 4 neutropenia are higher with other chemotheraphy regimens like CDDP plus Hydroxyurea, CDDP plus Paclitaxel, CDDP plus 5FU. In our study T.Capecitabine is well tolerated with less side effects. The drug concentrating effect and sensitizing effect also comparable with that of other regimens. Importantly the grade 5 toxicities are reported in most of the institution trails. Our study does not have any grade 5 toxicities. The rate grade 5 mucositis osteoradionecrosis and carotid blow out occurs in some of the patients in other institution trails. In our study there is no adverse events like carotid blow out, osteoradionecrosis, fibrosis of constrictor muscles and cervical fibrosis.

A multi institutional trail of RTOG 9610 published in 2007. This trial used 5FU and hydroxyurea weekly regimen with 60GY of RT. The acute toxicity reported in 17.6% grade 4 and 7.6% in grade 5. This trail used 2cm margins for the gross tumour volume. The techniques used are both 2D and conformal technique. The interval between the radiation is one of the important factor determining the tolerance of the treatment and their toxicities. Patients whose treatment interval time greater than three years will tolerate better with another full dose of radiation dose comparing to the other patients interval doses. The patient who undergone reirradiation >1year had good response and less

toxicity compared to the patients undergone reirradiation <1year. The results are comparable with the study and our study even has less toxicity than RTOG study. In most of the studies investigators recommended tight margins for the radiation field. In the study conducted by Gustave roussy they followed a protocol of providing 2cms margins around the tumour. But there is a confusion regarding the margins and the toxicities associated. If the spinal cord, brainstem, optic nerve, eyes involved in the planned field then it is important to consider tight margins instead of providing margins. If we compare other literature studies there is divergence in the tumour histology selected, treatment modalities offered, tumour localization, patient selected and techniques used.

Most of the investigators tried to identify the various prognostic markers associated with the reirradiation. The tumour size, interval time period between primary and secondary irradiation, total dose of secondary radiation dose. In some institutions they analyzed the tumour volume and field size as prognostic indicator. The total dose >60GY in our institution trail samples have better outcome and tolerability than comparing the other research trails. We found some prognostic correlation among the tumour volume and tumour field size. This is due to the toxicities associated with the field size and the involvement of normal tissues in the field.

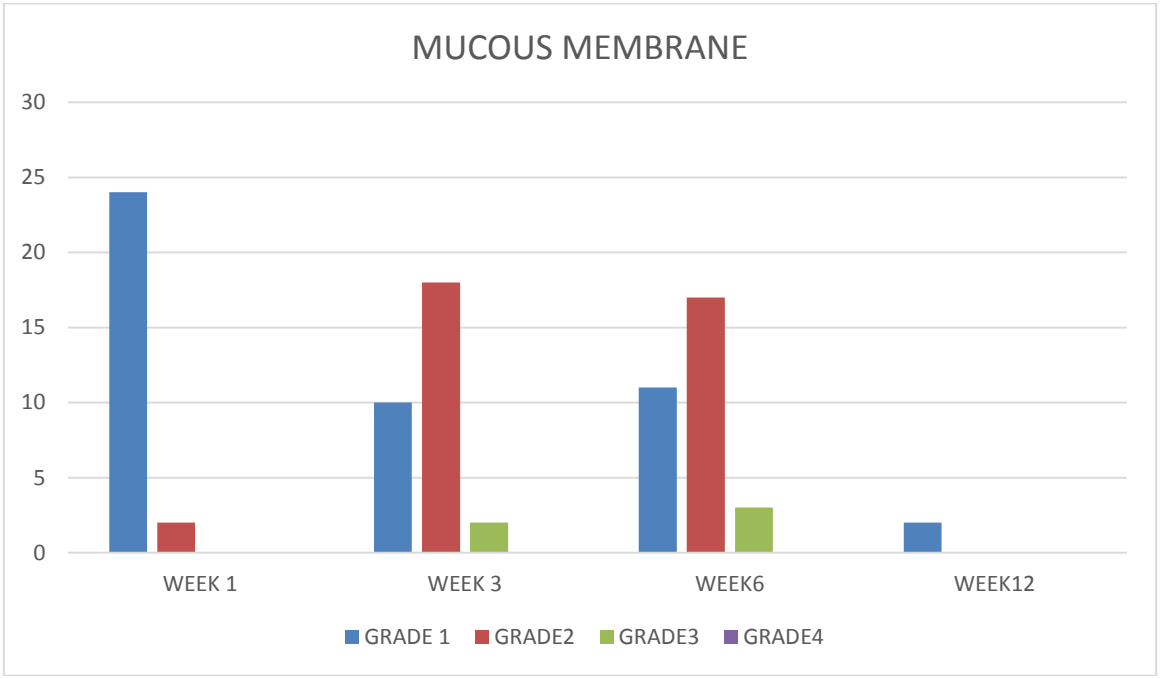
Importantly the higher the dose of radiation is required for getting increased response. The chemotheraphy which potentiates the sensitizing effect and individual cumulative tumouricidal dose with less side effects is important for the better response. Cumulative dose applied to the spinal cord is important determinant for field planning and in regards to toxicity. Recent radiobiological data suggest some regenerative capacity of spinal cord. The spinal cord have some memory regarding the dose of the radiation received previously. It has been suggested that the memory decreases as the time increases. It is estimated that the radiation-induced myelopathy rate at 60 Gy is about 5% [42] and these findings were taken into account for the specification of maximum dose limits in our study

CONCLUSION

Conclusion

Loco-regional failure of HNSCC in previously irradiated areas are bit a complicated. After a full course of (chemo) radiation it pose a challenging problem. For radiation oncologists, it remain potentially curable diseases in selected cases provided with favourable tumour biology. Whenever feasible, salvage surgery remains the standard of care. The feasibility remains approximately 20% of the cases. In case of adverse prognostic factors, immediate postoperative (chemo-) re-irradiation after salvage surgery can be administered safely and significantly improves loco-regional control. Despite relatively high rates of late radiation-induced complications, adjuvant (chemo-) re-irradiation should be considered in case there is an increased risk on locoregional recurrence, such as in case of positive surgical margins and/or lymph node metastases with Extra nodal spread. In case of unresectable locoregional failures curatively intended (chemo-) radiation should be considered in well-selected cases. We conclude that the use of full dose radiation along with T.Capecitabine is feasible in recurrent unresectable head and neck cancers. The incidence and severity of toxicities are acceptable in our study when compared to other studies. But

generally the toxicities due to reirradiation is high compared to the toxicity of primary radiation. The life threatening complications are rare. In this approach we can expect some long term survivors with complete response. At last when compared to chemotherapy alone the disease free survival, overall survival, response rates are better with reirradiation.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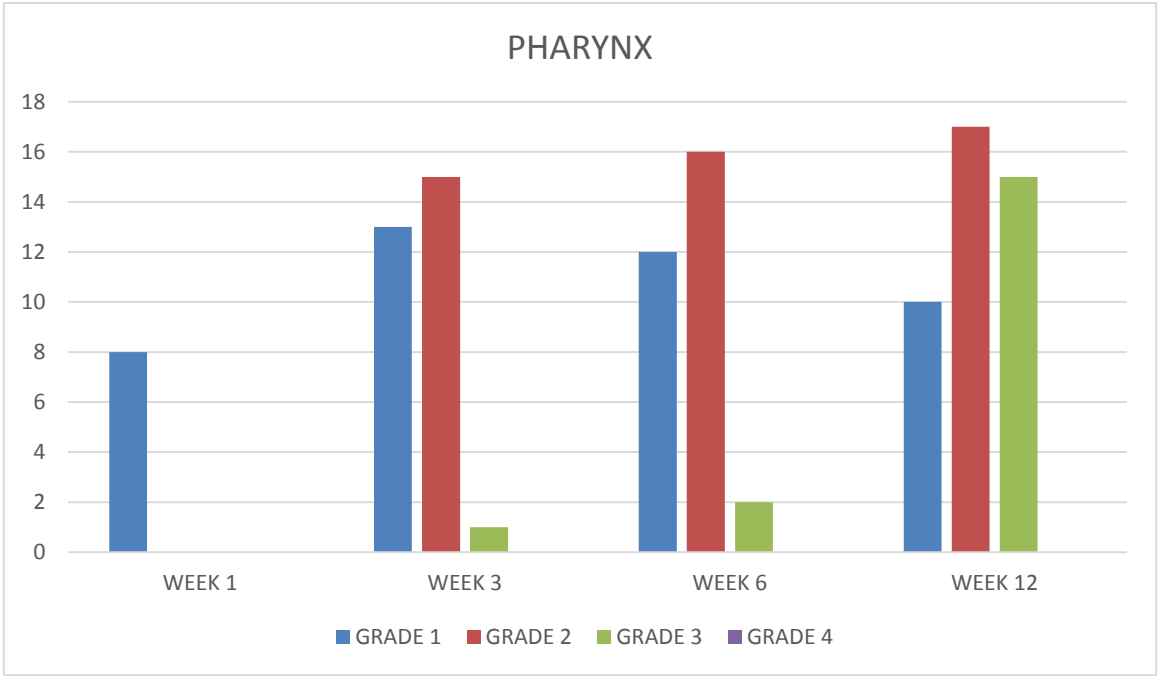
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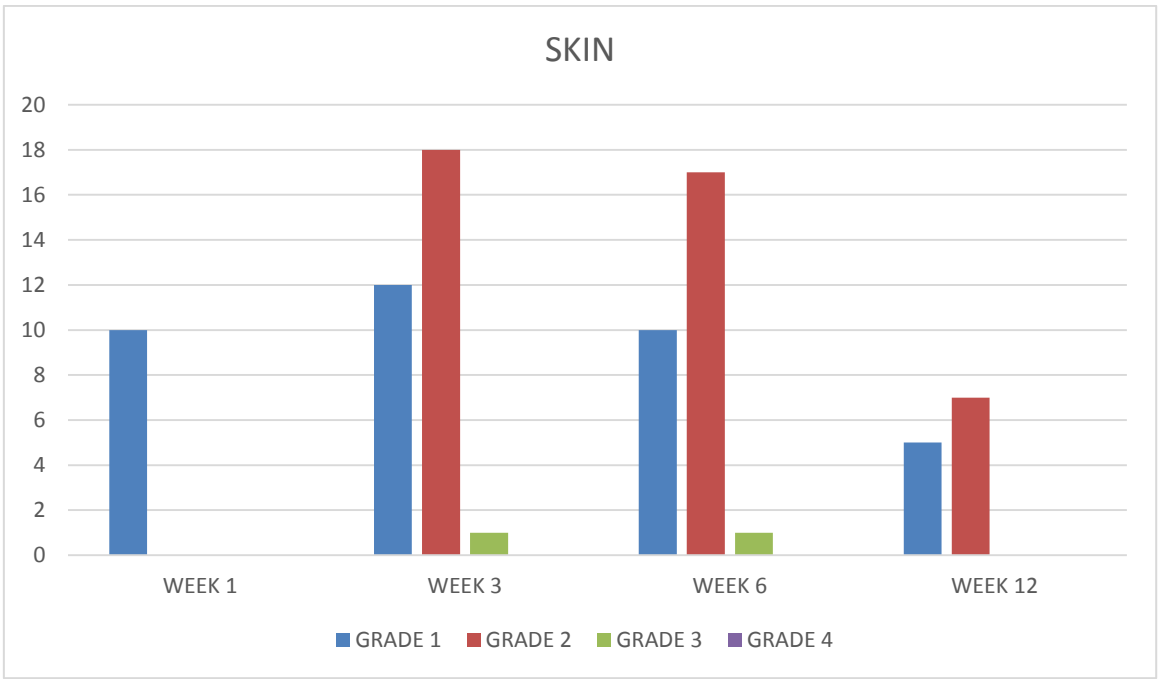
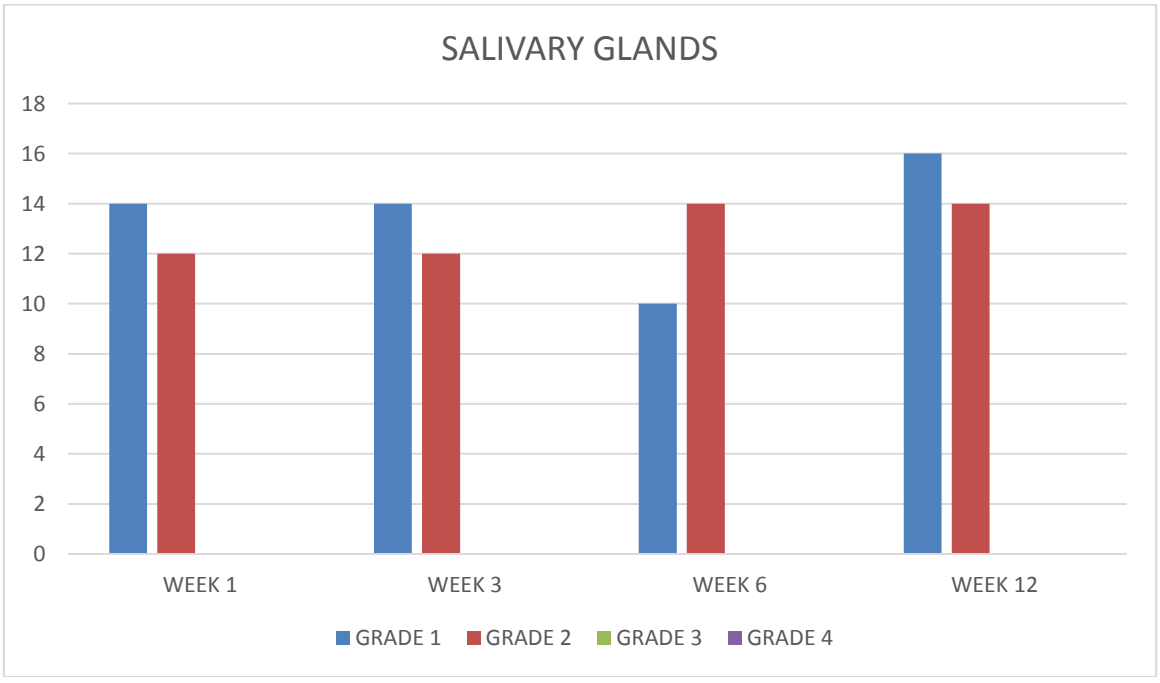
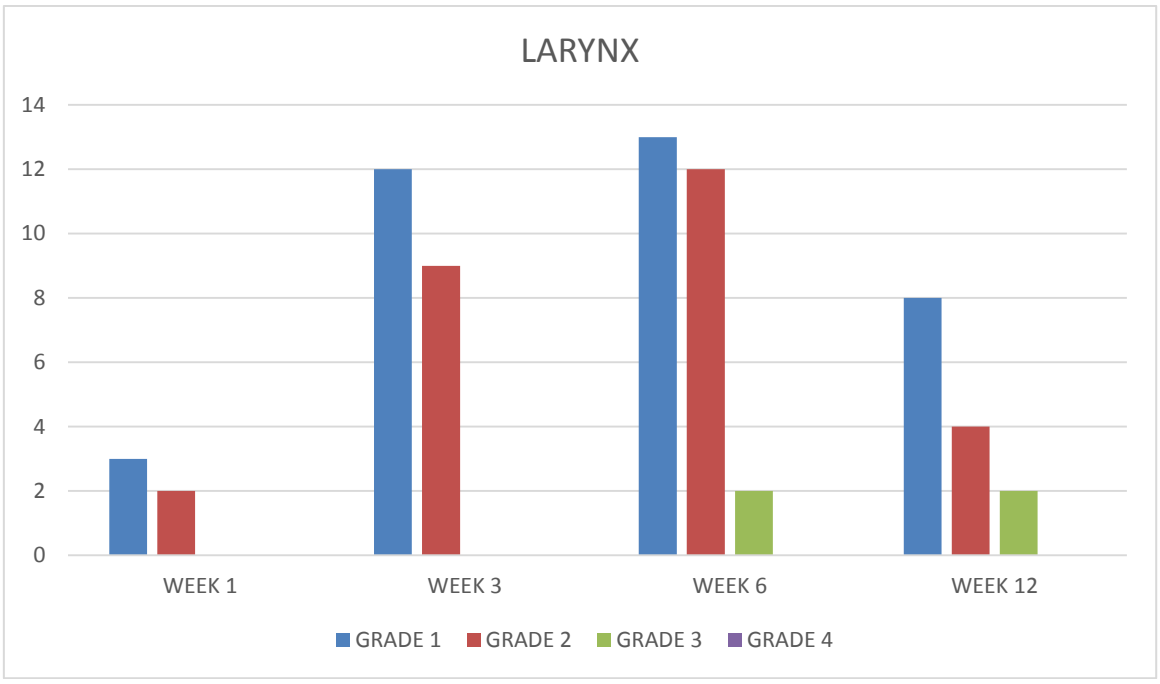


SALIVARY GLAND:

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GRADE 4

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INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.Durga Prasad.R.
Post Graduate Degree in Radio Therapy
Madras Medical College
Chennai 600 003

Dear Dr.Durga Prasad.R.

The Institutional Ethics Committee has considered your request and approved your study titled " **REIRADIATION WITH CONCURRENT CHEMOTHERAPY IN UNRESECTABLE RECURRENT HEAD AND NECK SQUAMOUS CELL CARCINOMA** " NO.05032015.

The following members of Ethics Committee were present in the meeting hold on 03.03.2015 conducted at Madras Medical College, Chennai 3

1. Prof.C.Rajendran, MD	:Chairperson
2. Prof.R.Vimala,MD.,Dean,MMC,Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi,MD.,Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.R.Nandini,MD.,Inst.of Pharmacology,MMC	: Member
5. Prof.K.Ramadevi, Director ,Inst.of Bio-Chem.MMC	: Member
6. Prof.Saraswathy,MD.,Director,Pathology, MMC	: Member
7. Prof.S.G.Sivachidambaram,MD.,Director I/c Inst.of Internal Medicine,MMC	: Member
8. Thiru S.Rameshkumar, B.Com., MBA.	: Lay Person
9. Thiru S.Govindasamy, BA., BL.,	: Lawyer
10.Tmt.Arnold Saulina, MA., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

23/3/15

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE

Sys 2

ஆய்வு தலைப்பு

தலை மற்றும் கழுத்துப்பகுதியில் மறுமுறை வரும் புற்றுநோய்க்கு நோய்குறி தணிப்பு மறுசுதிர்வீச்ச சிகிச்சையுடன் கதிர்வீச்சின் பயனை அதிகரிக்கவுய கேப்சிட்டபைன் என்னும் மாத்திரை உட்கொள்ளுதல்

ஆய்வாளர் :

பங்கேற்பாளர் :

இந்த ஆய்வு ராஜிவ் காந்தி அரசு பொது மருத்துவமனையில் நடைபெற உள்ளது. நீங்களும் இந்த ஆய்வில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதிலுள்ள தகவலின் அடிப்படையில் இந்த ஆய்வில் பங்கேற்பதா அல்லது வேண்டாமா என்று நீங்கள் முடிவு செய்து கொள்ளலாம். உங்களது சந்தேகங்களை எங்களிடம் கேட்டு நிவர்த்தி செய்து கொள்ளலாம்.

இந்த ஆய்வின் நோக்கம்:

மாறிவரும் பொருளாதார காரணிகள் மற்றும் வாழ்க்கைமுறையின் காரணமாக தலை மற்றும் கழுத்துப்பகுதி புற்றுநோயினால் பாதிக்கப்பட்டவர்களின் எண்ணிக்கை சமீபகாலமாக அதிகரித்துக்கொண்டே வருகிறது.

அப்பகுதியில் குணப்படுத்தக்கூடிய சிகிச்சை அளித்தாலும் மறுமுறை புற்றுநோய் கட்டிகள் உருவாகின்றன. அதனால் நோய்க்குறி தணிப்பு வைத்திய முறைகளை மட்டுமே பயன்படுத்தும் நிலைக்கு ஆளாகின்றனர். இவ்வகையான வைத்தியத்தில் பலவகை உள்ளன. இந்த ஆய்வில் பயன்படுத்தும் வைத்திய முறையின் மூலம் சிறந்த நோய்க்குறி தணிப்பையும் குறைவான பின்விளைவுகளையும் பெரும் வகையில் வழி செய்வதே எங்கள் நோக்கமாகும்.

ஆய்வின் செயல்முறை:

நோயாளிகள் இரத்தப் பரிசோதனை, முகம் மற்றும் கழுத்துப்பகுதி சி.டி.ஸ்கேன், நெஞ்சுப்பகுதி எக்ஸ்-ரே, பல் சுத்தம் மற்றும் பாதுகாப்பு, புகைப்பழக்கத்தை கைவிட ஆலோசனை முதலியவற்றை மேற்கொள்ள வேண்டும். இவை அனைத்தும் வழக்கமாக எல்லா புற்றுநோயாளிகளிடமும் நோயின் நிலையை அறிய மேற்கொள்பவையே. நோயாளிகளுக்கு தினமும் ஒருமுறை 6-7 வாரங்களுக்கு நோய்குறி தணிப்பு மறுசுதிர்வீச்சுடன் வாரம் ஒருமுறை கேப்சிட்டபைன் எனும் மாத்திரை கொடுக்கப்படும்.

ஆறு வாரங்கள் கழித்து நோயின் நிலையை அறிய சி.டி.ஸ்கேன் மற்றும் உடல் பரிசோதனை செய்யப்படும். இந்த பரிசோதனைகள் இவ்வகையான வைத்தியத்தின் விளைவுகள் மற்றும் பயன்களை அறிய அவசியம்.

ஆய்வினால் ஏற்படும் நன்மைகள்

சிறந்த நோய்க்குறி தனிப்பும், குறைவான பின்விளைவுகளும் கிடைக்க அதிக வாய்ப்புகள் உள்ளன.

ஆய்வினால் ஏற்படும் தீமைகள்

வழக்கமான கதிர்வீச்சுகளில் வரும் விளைவுகளைவிட அதிகம் ஏதுமில்லை.

ஆய்வினால் பிறருக்கு ஏற்படும் நன்மைகள்:

இந்த ஆய்வில் கலந்துகொள்வதன் மூலமாக நீங்கள் நோயின் தன்மையில் முன்னேற்றம் பெறலாம். மேலும் வருங்காலத்தில் பிற நோயாளிகளும் பயன்பெற இந்த ஆய்வு உதவியாக அமையும்.

மருத்துவ சிகிச்சையின் தகவல்கள் குறித்து விவரங்கள்:

உங்கள் மருத்துவ சிகிச்சை குறித்த தகவல்கள் ரகசியமாக பாதுகாக்கப்படும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுக்கு பரிசோதனைகள் செய்து அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :

இடம் :

INFORMATION TO PARTICIPANTS

TITLE: "REIRRADIATION WITH CONCURRENT CHEMOTHERAPHY FOR LOCOREGIONALLY UNRESECTABLE RECURRENT HEAD AND NECK CANCER"

Principal investigator: Dr.DURGA PRASAD.R

Name of the participant:

Site: Department of Radiotherapy, Madras Medical College & RGGGH, Chennai-3.

You are invited to take part in the research/study/procedure. The information in this document is meant to help you decide whether or not to take part.Please feel free to ask if any queries.

What is the purpose of the study?The incidence of head and neck cancer has been increasing worldwide .Local recurrences is a major problem after intensive curative treatment.With our treatment methodology we are aiming to give a better quality of life for the disease by achieving a better immediate locoregional response and less treatment related toxicity.

We have obtained permission from the Institutional Ethics Committee.

The study design: Single arm prospective study.

Study procedures: Patients will need to undergo blood investigations, CT scan neck, Xray chest, dental prophylaxis and smoking cessation counselling, if smoker which were done routinely in all head and neck cancer patients. These tests are essential to assess the status of the disease. Patients are treated with Reirradiation in conventional regimen over 6-7weeks along with Tab Capecitabine on treatment days. This is followed by assessment for toxicity and response after 6weeks. Patient will undergo clinical examination, laryngoscopy and ct scan neck for this.These tests are essential to assess the efficacy of treatment.

Possible risks to you: None greater than patients receiving standard radiotherapy.

Possible benefits to you: Better response at the tumour less toxicity from treatment.

Possible benefits to other people: The results of the research mat provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefits to future patients.

Confidentiality of the information obtained from you: You have the right to confidentiality regarding the privacy of your medical information[personal details, physical examination, investigations and your medical history]. B y signing this document you will be allowing the research team investigators, other study personal, Institutional ethics committee and any person

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent

Name _____ Signature_____ Date_____

INFORMED CONSENT FORM

TITLE OF THE STUDY:**"REIRRADIATION WITH CONCURRENT CHEMOTHERAPHY FOR LOCOREGIONALLY UNRESECTABLE RECURRENT HEAD AND NECK CANCER"**

NAME OF THE PARTICIPANT:
NAME OF THE PRINCIPAL INVESTIGATOR: DR. R.DURGA PRASAD,
NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

I_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising myfree power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms. *
8. I have not participated in any research study within the past 12month(s). *
9. I agree to undergo complete blood count, renal and liver function test, chest x ray, CT scan of the head and neck
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

or agency required by law like the drug controller general of India to view your data, if required.The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution.You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stopparticipating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at time during the course of the study without giving any reasons. You will still continue to receive the standard treatment if you decide so. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of investigator

Date:

Signature of the participant

Date:

Popovtzer et al. (2009)	Retrospective	Recurrent squamous cell head and neck cancer	31 out of 66 in the study	Minimum 6 months, median 37 months[a]	Total dose 70 Gy at 1.25 Gy b.i.d. with concurrent cisplatin and 5-FU	Acute grade III–V in 10%. Late grade III–V in 29%	Approximately 19 months (estimated from the published graph)[a]
Benchalal et al. (1995)	Pilot study	Head and neck cancer	19	Minimum 9 months, median 30 months	Total dose 60 Gy at 1.2 Gy b.i.d.	Acute grade III toxicity in 47%. Late grade III toxicity in 11%	Approximately 18 months (estimated from the published graph)

Spencer et al. (2008)	Multi-institutional prospective trial RTOG 9610	Unresectable recurrent squamous cell carcinoma of the head and neck	79	Minimum 0.6 years, median 2.5 years	4 Weekly cycles of chemoradiotherapy separated by 1 week of rest; 1.5 Gy b.i.d., total dose 60 Gy	6 deaths in acute period, acute grade IV in 18%, late grade III and IV in 22%, feeding tube at last follow-up in 70%	8.5
Watkins et al. (2009)	Retrospective	Locoregionally recurrent head and neck tumors	39	Minimum 0.5 years, median [illegible]	4 Weekly cycles of chemoradiotherapy separated by 1 week of rest; 1.5 Gy b.i.d., total [illegible]	4 deaths in acute period, acute grade IV in 10%, late grade III–V in 56%	19

Table 1. Selected chemotherapy trials for locally recurrent and metastatic head and neck cancer

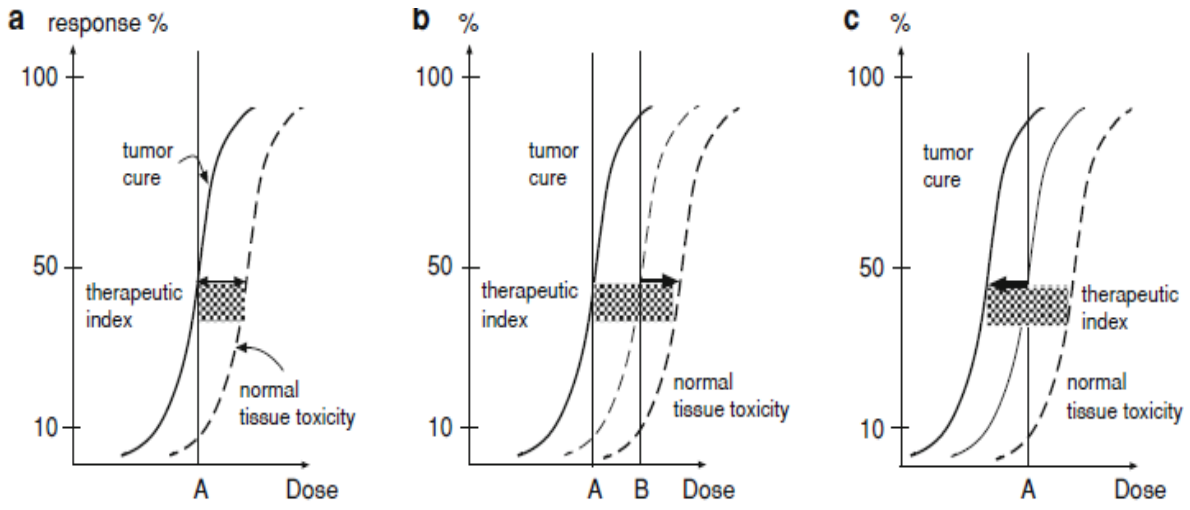
Investigators	Patients (*n*)	Regimen	Response rate (%)	MS (mo)
Forastiere *et al.* (3)	87	Cisplatin + 5-FU	87	6.6
Forastiere *et al.* (3)	86	Carboplatin + 5-FU	86	5.0
Forastiere *et al.* (3)	88	Methotrexate	10	5.6
Burtness *et al.* (4)	57	Cisplatin + cetuximab	35	9.2
Soulieres *et al.* (5)	115	Erlotinib	4	6.0
Bentzen *et al.* (6)	32	Paclitaxel + capecitabine	42	8.0
Vermorken *et al.* (7)	222	PF + cetuximab	36	10.1

Table 2. Selected re-irradiation trials for locally recurrent head-and-neck cancer

Investigators	Patients (*n*)	Chemotherapy	Median radiation dose (Gy)	Median follow-up (mo)	LRC (%)	MS (mo)
De Crevoisier *et al.* (8)	169	Some	60	70	NA	10
Haraf *et al.* (34)	45	Yes	50	41	20	8.5
Spencer *et al.* (10)	81	Yes	60	23	NA	8.5
Langer *et al.* (11)	105	Yes	60	24	NA	12.1
Salama *et al.* (23)	115	Yes	65	67	51	11
Lee *et al.* (16)	105	Some	59	35	42	15
Sulman *et al.* (26)	78	Some	60	25	64	28
Watkins *et al.* (30)	39	Yes	60	25	31	19
Dawson *et al.* (24)	60	Some	60	60	29	13
Popovtzer *et al.* (35)	66	Some	68	42	19	NA

Table 4. Chemotherapy regimens used with concurrent radiotherapy for locally recurrent head and neck cancer

Investigators	Chemotherapy regimen	Radiation dose (Gy)	Fractionation	RT split
Haraf *et al.* (34)	Hydroxyurea, 5-FU (± cisplatin)	60	Conventional	No
Spencer *et al.* (10)	Hydroxyurea, 5-FU	60	Hyperfractionated	Yes
Langer *et al.* (11)	Paclitaxel, cisplatin	60	Hyperfractionated	Yes
Watkins *et al.* (30)	Hydroxyurea, 5-FU	60	Hyperfractionated	Yes
Watkins *et al.* (30)	Paclitaxel, cisplatin	60	Hyperfractionated	Yes
Lee *et al.* (16)	Cisplatin	59	Conventional	No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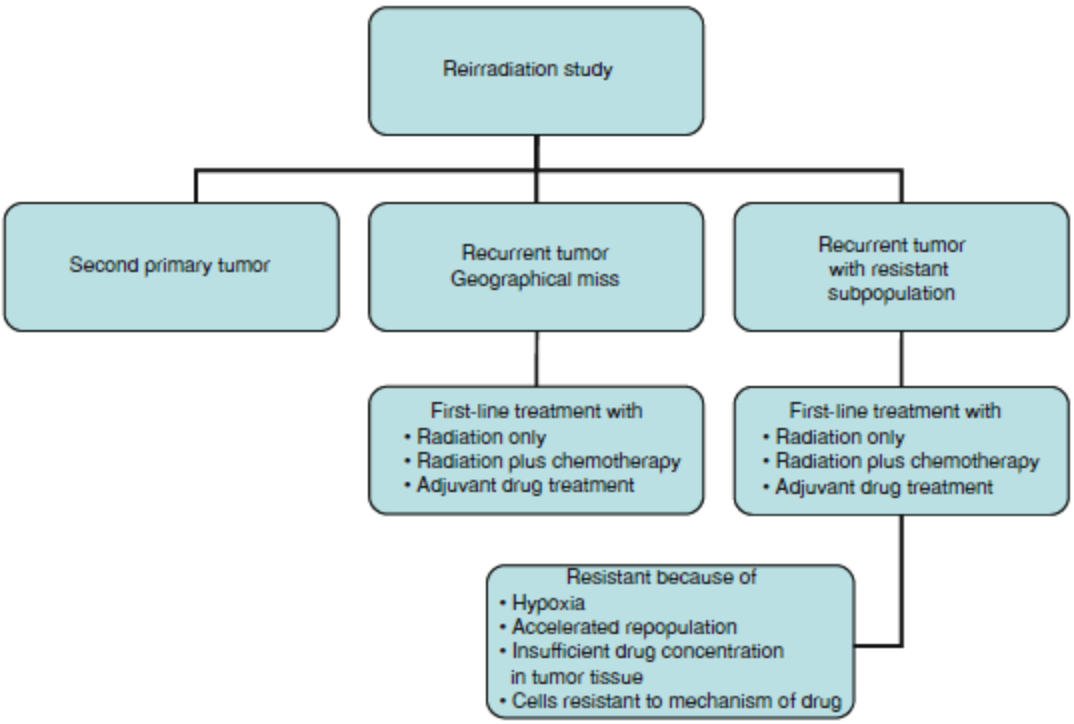
Reirradiation study
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Recurrent tumor
with resistant
subpopulation
First-line treatment with
• Radiation only
• Radiation plus chemotherapy
• Adjuvant drug treatment
First-line treatment with
• Radiation only
• Radiation plus chemotherapy
• Adjuvant drug treatment
Resistant because of
• Hypoxia
• Accelerated repopulation
• Insufficient drug concentration
in tumor tissue
• Cells resistant to mechanism of drug

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TITLE

REIRRADIATION WITH CONCURRENT CHEMOTHERAPHY FOR LOCOREGIONALLY UNRESECTABLE RECURRENT HEAD AND NECK CANCER"

DEPARTMENT OF RADIOTHERAPY

MADRAS MEDICAL COLLEGE